THE TOXICOLOGY OF SALVARSAN:

DIOXYDIAMIDO-ARSENO-BENZOL (SALVARSAN
OR KHARSIVAN).

BY

WILLIAM HENRY WILLCOX, M.D.LOND.,

B.Sc.LOND., F.R.C.P.LOND.,

LIEUTENANT-COLONEL R.A.M.C.; PHYSICIAN TO OUT-PATIENTS,
ST. MARY'S HOSPITAL, LONDON; SENIOR SCIENTIFIC
ANALYST TO THE HOME OFFICE;

AND

JOHN WEBSTER, F.I.C.,

ASSISTANT SCIENTIFIC ANALYST TO THE HOME OFFICE; DEMONSTRATOR
OF PATHOLOGICAL CHEMISTRY TO ST. MARY'S HOSPITAL
MEDICAL SCHOOL, LONDON, W.

Dioxydiamido-arseno-benzoldihydrochloride is the chemical name for a most valuable therapeutic remedy, and it is better known by the name "salvarsan," or "kharsivan"—the latter denoting the English preparation.

Salvarsan was introduced by Professor Paul Ehrlich in 1910, and neo-salvarsan in 1912. They were also known by the respective numbers "606" and "914," these denoting the numerical position of the compounds in the list of chemical substances prepared and experimented upon.

On the outbreak of war it was found desirable that dioxydiamido-arseno-benzol should be manufactured in this country. The preparation of this important remedy was satisfactorily carried out, and it was introduced under the name of "kharsivan." Before being placed on the market samples of kharsivan were submitted to careful chemical and physical tests, and these gave practically identical results with salvarsan.

Physiological and therapeutic tests were carried out by one of us (W. H. Willcox) at the request of the Board of Trade, and it was found that the English preparation was practically identical in its physiological and therapeutic effects with salvarsan. The toxic action of kharsivan was certainly not greater than that of salvarsan.

Kharsivan was then definitely introduced after the sanction of the Board of Trade had been received. The testing of kharsivan after its introduction was entrusted to the Medical Research Committee, who have submitted samples of every batch prepared to searching physiological and toxicological tests.

USES.

Syphilis.

Salvarsan, or kharsivan, has become definitely established as the most effectual remedy for the treatment of syphilis.

The recent discovery in 1905 of the causal agent of syphilis—namely, the *Spirochaeta pallida*—has enabled this organism to be demonstrated in the lesions associated with syphilis. The special serum test—the Wassermann reaction—published in 1906, enabled the presence of a syphilitic infection to be demonstrated in the blood serum, and in the cerebro-spinal fluid in cases where the central nervous system was involved.

The therapeutic effect of any antisyphilitic remedy can be definitely estimated by the application of tests for the presence of the specific organism in syphilitic lesions, and by the application of the Wassermann reaction to the blood serum.

It is by these tests that it has been definitely proved that salvarsan or kharsivan are the remedies which occupy the foremost place in the treatment and cure of syphilis.

It is unnecessary to emphasize the importance of these remedies from a prophylactic point of view, since the rapid destruction of the infective agent in the body means the prevention of spread of infection.

Other Spirochaete Infections.

Other spirochaete infections, such as relapsing fever in man, due to a spirochaete infection; recurrent fever in animals, due to spirochaetes; and spirillose infection of birds, respond equally well to the administration of salvarsan or kharsivan in proper doses.

Yaws is a disease due to a spirochaete infection, and this responds rapidly to treatment with salvarsan or kharsivan.

Mycosis fungoides and glandular conditions resembling syphilis have shown marked benefit after treatment with salvarsan or kharsivan.

Tertian malaria has been cured by the administration of these remedies, but quartan malaria does not seem to respond to treatment in the same way.

Salvarsan, or kharsivan, has been used with benefit in leukaemia, pernicious anaemia, lymphadenoma, trypanosomiasis, anthrax, psoriasis, and lichen planus, but the effect has not been of so marked a degree as in the spirochaete infections above named.

CONSTITUTION AND PROPERTIES.

Salvarsan, or kharsivan, has the chemical formula:

This may be expressed graphically thus:

Salvarsan is seen to be a complex compound of arsenic with the benzene nucleus.

It was evolved after a great deal of experimental work extending over a number of years. Koch had found that ordinary antiseptic drugs which were of high value outside the body were useless *in vivo* since they had as powerful a toxic action on the organism as on the parasite; or otherwise expressed, their organotropic action was equal to their parasitotropic action. Ehrlich endeavoured to find a drug which had as high a parasitotropic but as low as organotropic action as possible. He found that the best results were yielded by compounds of arsenic with the benzene nucleus.

Atoxyl was an example of one of these compounds. Its constitution is expressed by the formula:

Koch found that this drug was markedly parasitotropic in sleeping sickness, and that the organotropic action was low. He spoke highly of the value of atoxyl.

When atoxyl came to be extensively used on man it was soon found that the drug had a peculiar organotropic action in some cases, which completely contraindicated the use of the drug altogether. It had an organotropic action for the optic nerve and in some cases caused optic atrophy and complete blindness.

Further experiments on other compounds of arsenic and benzene led to the discovery by Ehrlich and his co-worker, Berthelm, of salvarsan; it was found to have a high parasitotropic action in the body and a very low organotropic action. Salvarsan had no organotropic action on the optic nerves. A peculiarity of salvarsan is that the parasitotropic action on spirochaetes is much greater in the body than *in vitro*.

Salvarsan at the time of its introduction was the drug which, of all remedies known, gave the highest parasitotropic action for spirochaetes combined with the minimum organotropic action.

The introduction of this valuable remedy marked an epoch in the treatment of syphilis, and it was found that no other known drug compared in efficacy with salvarsan and its derivatives.

Salvarsan is a powder of a pale yellow colour. It contains arsenic in amount equal to 34 per cent. expressed as the metal arsenicum, or 44.9 per cent. expressed as arsenious oxide (As_2O_3).

It is soluble in water (1 in 5), forming an acid solution. It is soluble in methyl alcohol (1 in 3), and in ethyl alcohol (1 in 12). It is also soluble in glycerine. If salvarsan is dissolved in water and caustic soda solution

is cautiously added a precipitate forms, which redissolves on the addition of slight excess of the alkali.

Salvarsan is very unstable and decomposes on exposure to the atmosphere. It is sold in hermetically sealed glass tubes, which contain an inert gas in addition to the powder. In aqueous solution salvarsan rapidly decomposes.

Chemical Tests.

1. An aqueous solution of salvarsan, when treated with a stream of H_2S gas, yields no precipitate of arsenic sulphide even after the addition of hydrochloric acid and warming. This shows the absence of inorganic arsenic.

2. An aqueous solution of salvarsan gives with either ferric chloride solution or with bromine water a brown colour, becoming a deep crimson in a few seconds.

3. Ignite the solid substance in a test tube: the substance melts and chars, whitish fumes are given off, and a blackish sublimate forms on the tube. When cool the contents of the tube have an aromatic smell, like that of nitrobenzene.

4. An aqueous solution of salvarsan is placed in a test tube, which is cooled in ice. Some solution of nitrous acid is added till present in slight excess and the mixture left for twenty minutes. The excess of nitrous acid is removed by the addition of urea solution. The solution is divided into two parts:

- (a) To one part an alcoholic solution of alpha-naphthylamine is added; a beautiful violet colour results.
- (b) To the other part an alcoholic solution of beta-naphthylamine is added. No vermilion colour is produced, showing the absence of atoxyl.

5. *Reinsch Test.*—Salvarsan if submitted to this test gives a definite reaction for arsenic. The fact that the arsenic is present in organic combination does not prevent the detection of arsenic by this test.

6. *Marsh-Berzelius Test.*—Salvarsan gives an unsatisfactory result, since the organic combination of the arsenic prevents its detection by this test.

In order that the Marsh-Berzelius test may be accurately employed, it is necessary for the organic compound to be broken up. This can be done by oxidation in the usual manner with nitric and sulphuric acid, or by means of hydrochloric acid and potassium chlorate. In this way the arsenic is converted to arsenic acid. The oxidized solution should be reduced by treatment with potassium meta-bisulphite and dilute sulphuric acid and the excess of sulphur dioxide boiled off.

This solution now contains the arsenic in the form of arsenious acid, which can readily be detected or estimated by the Marsh-Berzelius test.

7. *Mirror Test.*—For quantitative estimations of minute amounts of salvarsan the mirror yielded by a given quantity of salvarsan, or an organ containing it, is compared with a series of standard mirrors obtained from known amounts of arsenious oxide.

The electrolytic method of the Marsh-Berzelius test is much the most satisfactory for toxicological work.

Physiological Tests.

Animals on which these may be conveniently employed are white mice, white rats, and rabbits.

A solution of salvarsan in normal saline is taken, and a solution of caustic soda is added until the precipitate which forms just redissolves. This solution is made up to a strength of 1 per cent. (1 gram in 100 c.cm.) It is slightly alkaline in reaction, and is used for injection into animals.

Mice.—These animals are susceptible to the toxic action of salvarsan.

The maximum dose borne without a fatal result is for a mouse weighing 20 grams, about 0.004 gram—that is, 0.2 gram per kilo. Of the 1 per cent. solution, 0.4 c.cm. is injected subcutaneously under the skin of the back, and by gentle massage with a glass rod the liquid is dispersed. No fatal result should follow the injection, but larger doses will probably cause death. Smaller doses—for example, 0.3 c.cm. and 0.2 c.cm.—should also be given. They should not produce a fatal result.

Rats.—These animals are very convenient for the application of toxicological tests, since they are less delicate than mice as regards susceptibility to shock, and

they are able to withstand larger doses per kilogram body weight.

For rats a curative dose in experimental spirochaete infections is 0.05 gram of salvarsan per kilogram body weight. In a rat weighing 100 grams a dose of salvarsan of 0.5 c.cm. of 1 per cent. solution—that is, 0.005 gram—causes no toxic symptoms. The solution is given subcutaneously as above.

In a rat weighing 100 grams a dose of salvarsan of 1.5 c.cm. of 1 per cent. solution—that is, 0.015 gram—is well borne and produces no toxic symptoms. (Dose = 0.15 gram per kilo.)

In a rat weighing 100 grams a dose of salvarsan of 3 c.cm.—that is, 0.03 gram—is borne without marked toxic symptoms. (Dose = 0.3 gram per kilo.)

In the above experiments local sloughs may occur at the site of injection after a few days. These usually heal up.

Rabbits.—Doses of salvarsan of 0.2 gram per kilogram body weight are borne without toxic effect if given subcutaneously, though subsequent local sloughing is likely to occur. A dose of 0.1 gram per kilogram body weight is well borne if given intravenously.

NEO-SALVARSAN.

This is a powder of a somewhat deeper yellow colour than salvarsan; it is less finely divided, and does not adhere to the sides of the capsule in which it is contained. It is more unstable than salvarsan, and its solution quickly decomposes, especially if heated.

Solutions of neo-salvarsan should be made in distilled water or in a weak saline solution (0.4 per cent.) and the temperature of the solution should not exceed 20° to 22° C.

Neo-salvarsan forms a neutral solution, and alkali should not be added to it before use.

Neo-salvarsan is salvarsan acid sodium formaldehyde sulphonylate. It has the formula:

Owing to the addition of the further chemical group in salvarsan, neo-salvarsan contains a lower percentage of arsenic. A dose of salvarsan must be multiplied by $\frac{2}{3}$ in order to get the corresponding dose of neo-salvarsan.

Thus 0.6 gram of salvarsan corresponds to 0.9 gram of neo-salvarsan.

Neo-salvarsan has the same physiological and therapeutic effects as salvarsan. The addition of the further chemical group to salvarsan considerably adds to the convenience and facility of administration without altering the therapeutic action of the new compound.

MODE OF ADMINISTRATION OF SALVARSAN AND NEO-SALVARSAN.

Subcutaneous and also intramuscular injections of solutions of these compounds were used, but a long experience has shown that intravenous injections are far preferable. They are more efficacious and attended with less risk if carefully given. There is much less pain and discomfort with intravenous than with the other modes of injection.

Subcutaneous and intramuscular injections are always associated with a good deal of local discomfort or pain, and in the experience of one of us (W. H. W.) local necrosis of the tissues at the site of injection is by no means uncommon. Also local inflammatory troubles may follow a subcutaneous or intramuscular injection; thus, one case in which an injection of salvarsan was given in the subscapular region developed a local pleurisy, with effusion at the site of the injection. This case was seen by one of us (W. H. W.).

Suspensions of salvarsan or neo-salvarsan in oily liquids have been recommended, but the absorption of the drugs in this mode of administration is uncertain and local troubles may follow, so that this method is certainly less desirable than the intravenous mode of administration.

PREPARATION OF SOLUTIONS.

For Intravenous Injections.

Salvarsan.—Salvarsan 0.6 gram is placed in a sterile glass flask containing 40 c.cm. of 0.5 per cent. sterile saline solution. The powder quickly dissolves on shaking. Some solution of pure caustic soda (15 per cent.) is added cautiously drop by drop until the precipitate which forms just redissolves. About 20 to 23 minims of the solution will be required. The liquid is now made up to 300 c.cm. with 0.5 per cent. saline solution. This solution is used for injection into a vein, the usual precautions being taken to prevent entry of air or escape of the arsenical solution into the subcutaneous tissue round the vein.

Neo-salvarsan.—Neo-salvarsan 0.9 gram is placed in a sterile flask, and 150 c.cm. of specially pure sterile normal saline (0.4 per cent.), of temperature not exceeding 22° C., are added. The neo-salvarsan readily dissolves, and the solution is ready for injection with the usual precautions.

For Intramuscular or Subcutaneous Injections.

Salvarsan 0.6 gram is triturated in a sterile mortar with 20 minims of a 15 per cent. caustic soda solution, 15 c.cm. of sterile distilled water are added, and one or two drops more of the caustic soda solution, if the liquid is not quite clear.

Neo-salvarsan 0.9 gram is dissolved in 18 c.cm. of sterile distilled water.

Precautions should be taken as to the purity of the distilled water used in the preparation of the saline solution and for dissolving the salvarsan or neo-salvarsan. The water should be freshly distilled and kept under perfectly aseptic conditions until required. It has been shown that if distilled water contains bacteria, the sterilization of it, while killing the bacteria, does not destroy the toxins present in them, and such water may cause a rise of temperature on intravenous injection quite apart from any toxic action of the salvarsan or neo-salvarsan.¹

SYMPTOMS FOLLOWING AN INTRAVENOUS INJECTION
OF SALVARSAN OR NEO-SALVARSAN.*Slight Symptoms.*

The patient should be resting in bed during the injection and for twenty-four hours afterwards. With this precaution in a number of cases no symptoms of any kind occur.

It is common, however, for slight symptoms to occur, although every care may have been taken in the preparation and administration of the solution. Thus, nausea for a few hours after the injection and occasionally vomiting are common. A rise of temperature of one or two degrees Fahrenheit, within a few hours of the injection is common. Slight headache often occurs, but this in most cases is probably the result of the rise of temperature. A slight diarrhoea—for example, two or three actions of the bowels within twenty-four hours of the injection—is not uncommon.

The above symptoms are all that occur in the great majority of cases.

Slight albuminuria for one or two days after an injection has occurred on rare occasions.

Thrombosis in the course of the vein into which the injection has been given is of rare occurrence, but has been seen by one of us (W. H. W.).

Marked pyrexia occasionally follows an injection—for example, a rise of three or four degrees Fahrenheit or even more. This may last for a few days without other marked symptoms. It has been suggested that this rise of temperature is due to the endotoxins liberated by the destructive action of the salvarsan on the spirochaetes in the body.

Shock during, or immediately after, an injection has occurred, but is very uncommon. In a recent case a fatal result occurred during the course of an injection, although every care had been taken.

Severe Symptoms.

These are of two types:

I. Symptoms of Arsenical Poisoning.

Very occasionally symptoms of acute arsenical poisoning follow an injection of salvarsan. Thus some shivering or a rigor may follow an injection; there will be a rise of temperature; headache and some pains in the limbs,

nausea and vomiting, with furred tongue and diarrhoea, may occur. The conjunctivae are injected, and in some cases subconjunctival haemorrhages occur. An erythematous rash and slight jaundice occur in these cases. The patient becomes somewhat delirious, and stupor may supervene. The urine contains albumin and some granular casts, and traces of bile are present in cases with jaundice.

II. Symptoms of Profound Toxaemia.

This is the type of case which is usually attended with a fatal result.

Details of the symptoms are given in some of the cases enumerated below. Within three days of the injection of salvarsan dangerous nervous symptoms supervene—for example, collapse and abnormal mental condition. In one case acute pain in the abdomen and pain at the back of the neck were complained of. The patient becomes stuporose with twitchings of the muscles, and epileptiform convulsions are likely to occur. Coma intervenes, with collapse and death. The pupils are often dilated and the reflexes absent. The prognosis is very grave in cases of this type. The urine is usually markedly diminished in quantity and contains albumin and casts.

The pathology of cases of this kind is difficult to understand. After careful consideration it appears that the symptoms are really due to a profound autointoxication, such as occurs in uraemia. This view is borne out by the occurrence of degenerative changes in the liver, heart, and kidneys which are found on *post-mortem* examination in these cases.

The symptoms are not to be explained by anaphylaxis due to the setting free of endotoxins consequent on the destruction of spirochaetes, since the latent period (three days or more) in some of the cases is quite incompatible with this explanation.

Most of the deaths from salvarsan or neo-salvarsan are of this type, and it is important that every safeguard should be taken to avoid catastrophes of this nature.

Post-mortem Signs in Cases of Death after Salvarsan.

There is little of a definite nature to be found in these cases beyond degenerative changes of a fatty nature, or cloudy swelling, in the heart, liver, and kidneys. In some cases death has been due to a local lesion—for example, haemorrhage from a cerebral vessel.

EXCRETION OF SALVARSAN AND TOXICOLOGICAL ANALYSES.

After an injection of salvarsan arsenic is found in the blood. Thus, one hour after the injection of 0.6 gram there was found respectively in two cases $\frac{1}{2}$ mg. and $\frac{1}{3}$ mg. of arsenic (calculated as As_2O_3) in 100 c.cm. of blood serum. The blood clot was found to be almost free of arsenic, this being found only in the blood serum.

Salvarsan is excreted mainly by the kidney and bowel. Arsenic is present in the urine and faeces for at least three weeks after an intravenous injection.

In cases of death after salvarsan arsenic is found in the abdominal viscera—for example, spleen, kidney, liver, suprarenal glands, etc. It is also found in small amounts in the muscles and blood.

A most interesting feature is that arsenic seems to be almost entirely absent from the brain and nervous system, so that the symptoms of profound toxaemia in cases of salvarsan poisoning are certainly not due to the action of the arsenic as such on the central nervous system.

SALVARSAN IN LACTATION.

To investigate the influence of salvarsan on the milk of a lactating woman to whom the drug has been administered, the milk from a woman to whom two intravenous injections of salvarsan were given was collected. The first specimen was taken 72 hours after the first injection (0.4 gram) had been given; the second specimen was collected 12 hours after the second injection, of 0.5 gram. Both of these specimens were found to be free from arsenic.

In a second woman to whom 0.5 gram of salvarsan had been given, samples of milk were collected 5½ hours, 10½ hours, 16 hours, 36 hours and 60 hours respectively after the injection. Arsenic was entirely absent from all these samples, though the most delicate tests were employed.

It thus appears certain that the benefits resulting in a

syphilitic baby who is suckling from an infected mother, to whom salvarsan is given, cannot be due to the presence of salvarsan in the milk ingested by the baby. Any improvement in the child's health in such a case is to be explained on other grounds—for example, the presence of antibodies in the mother's milk, consequent on the destruction of spirochaetes in her body as a result of her injection of salvarsan.

PRECAUTIONS IN THE ADMINISTRATION OF SALVARSAN.

It must be remembered that salvarsan and neo-salvarsan are compounds having a powerful therapeutic action, and that in some patients, in spite of all precautions that may be taken, certain toxic symptoms will develop.

The susceptibility to salvarsan of patients with sound bodily organs and in good health undoubtedly varies very much, and in a susceptible person an average dose of salvarsan may produce alarming and even dangerous symptoms. Fortunately this idiosyncrasy to the effects of salvarsan is not common in healthy people.

CONTRAINDICATIONS.

Renal Disease.

Renal disease is a contraindication to the use of salvarsan. A careful clinical examination for symptoms of the condition should be made, and also a careful examination of the urine should be carried out. It is important to note the daily quantity of urine excreted, the specific gravity, the percentage and daily quantity of urea and chlorides, and especially the presence of albumin or casts. Renal inadequacy as shown by a low figure for urea and chlorides adds to the risk of toxic symptoms from salvarsan. The presence of albumin and casts in the urine will usually be a contraindication for the administration of salvarsan. The important question to be considered is the excretory efficiency of the kidney, and if this is poor, then, generally speaking, salvarsan should be avoided if possible.

In cases of albuminuria due to pyelitis or cystitis salvarsan may be given, provided that the renal excretion is good. The same view holds also with cases of functional or physiological albuminuria. There is undoubtedly risk in giving salvarsan in cases of acute and subacute nephritis, and also in parenchymatous and chronic interstitial nephritis.

In cases of albuminuria due to nephritis of syphilitic origin very careful consideration is necessary before salvarsan should be given. There is bound to be some risk, but the call for an efficient remedy to deal with an obstinate condition of this kind may be so great as to more than counterbalance the risk. It is always wise in these conditions to give a small dose of salvarsan—for example, 0.3 gram for an adult. This dose may be repeated in four weeks, and it may be increased if the first dose was well borne.

Circulatory System.

Where there is advanced heart disease and failure of compensation, salvarsan is contraindicated. The presence of a valvular lesion, provided that compensation is well maintained and the condition of the patient good, is not necessarily a contraindication.

In advanced degenerative conditions of the heart muscle there is risk of syncope from shock, and salvarsan should be avoided. In conditions of advanced arterio-sclerosis it is wise to avoid the use of the drug.

Respiratory System.

Serious bronchial conditions—for example, septic forms of severe bronchitis—are contraindications.

Nervous System.

Salvarsan is usually contraindicated in advanced degenerative conditions of the central nervous system. In meningitis of syphilitic origin the drug should be used with great caution, and should never be given in more than half doses.

Salvarsan has been used recently in the treatment of tabes and general paralysis of the insane. As a rule, the intravenous administration of the remedy does not directly do good except in early cases. The reason for this is that when salvarsan is administered intravenously the drug is not excreted by the choroid plexus and does not penetrate to the cerebro-spinal fluid, which remains free from arsenic.²

In order to overcome this difficulty, cases of tabes and general paralysis of the insane have been treated by giving salvarsan intravenously, afterwards withdrawing blood from a vein—for example:

- (1) At an interval of an hour or so; or
- (2) After an interval of a few days.

The serum is separated under aseptic conditions, and is injected into the spinal canal by lumbar puncture. In the former case (1) the serum will contain a small amount of salvarsan. In the latter case (2) the serum will contain perhaps a trace of salvarsan, but also antibodies.

Both methods have been attended with much greater success than the mere intravenous administration of salvarsan.

It is difficult to say whether the benefit from spinal injection of salvarsanized serum is due to direct action of salvarsan in the serum on the affected nervous tissues or to the action of the antibodies present. Probably both have an important beneficial action.

In cases in middle or advanced life, where there is a certain amount of arterio-sclerosis present and the blood gives a positive Wassermann reaction, the question often arises whether salvarsan should be administered. In cases of this kind it is well to avoid the use of the drug unless there is definite and unmistakable evidence of an active syphilitic lesion.

The presence of a positive Wassermann reaction, apart from any active syphilitic lesion, is not, in our opinion, a sufficient justification for the use of salvarsan in these cases.

The presence of any serious disease of any kind should always call for the greatest consideration before a full dose of salvarsan is given. It must be remembered that there is bound to be risk of the development of serious toxic symptoms.

INTERVALS BETWEEN SUCCESSIVE DOSES.

Toxicological analyses show that a full dose of salvarsan (0.6 gram) is not completely excreted after three weeks. Probably by this time only minute traces remain in the body.

We are strongly of opinion that an interval of four weeks should elapse between the administration of full doses of salvarsan. With shorter intervals there is risk of a cumulative action, since the second dose may be given while some of the former dose still remains in the abdominal viscera.

TREATMENT OF SALVARSAN TOXAEMIA.

Prophylactic treatment is most important.

An aperient should be given the night before the remedy is administered. Alcohol and tobacco should be avoided for twenty-four hours before and after the administration. The patient should remain in bed on the day in which the drug is given, and for twenty-four hours afterwards.

Slight symptoms—such as nausea, slight pyrexia, headache, etc.—call for nothing but the simplest remedies. Should the temperature remain above normal for more than a few hours, the patient should remain in bed until it has reached the normal line and remained there for twenty-four hours.

It is wise to diet patients carefully until all symptoms have cleared up. The diet should be light—for example, milk, milk puddings, fruit, vegetables, toast, bread, etc. Meat, meat extracts, soups, and alcohol should be avoided. Constipation should be avoided by giving suitable aperients.

Where serious symptoms occur—such as collapse, twitchings, stupor or delirium or coma—an intravenous injection of normal saline (2 to 3 pints) should be given, and repeated if necessary. Normal saline may also be given subcutaneously with advantage. Rectal injections of normal saline, containing 3 drachms of sodium bicarbonate to the pint, should be given every eight hours. Where the blood pressure is not low venesection should be done, and about 10 oz. of blood withdrawn. This should be followed by the giving of saline into the vein.

If the patient becomes comatose, it is important to continue nourishment by the mouth—for example, 15 oz. of peptonized or citrated milk should be given by a stomach or nasal tube every six hours. For collapse,

strychnine (gr. $\frac{1}{4}$) may be given hypodermically every four hours, and oxygen, or oxygen passed through alcohol, may be administered with advantage.

In the early onset of toxic symptoms the following mixture should be given:

Sodium citrate	...	...	...	...	5 j
Sodium bicarbonate	...	...	...	...	3 ss
Potass. citrate	...	...	...	...	3 ss
Caffeine citrate	...	...	...	...	gr. ii]
Syr. aurant.	...	...	...	...	5 j
Aq.	...	...	...	ad	5 j

Every three hours.

TOXICOLOGICAL ANALYSES AND CASES.

I. Analysis of Urine and Faeces.

CASE I.—P. L. June 2nd, 1911, 0.6 gram salvarsan given.

		Milligrams of Arsenic per 100 Grams.	
		Urine.	Faeces.
June 3	...	1.0	1.4
June 5	...	1.0	2.5
June 7	...	0.17	1.7
June 9	...	0.17	
June 10	...	0.07	

CASE II.—H. 0.5 gram salvarsan given October 12th, 1914.

No. of Days after Salvarsan.		Milligrams of As ₂ O ₃ in 100 c.cm. Urine.	
4	...	...	0.3
7	...	...	0.3
10	...	...	0.15
13	...	...	0.03

CASE III.—C. 0.5 gram salvarsan given October 14th, 1914.

No. of Days after Salvarsan.		Milligrams of As ₂ O ₃ in 100 c.cm. Urine.	
2	...	...	0.2
5	...	...	0.2
8	...	...	0.15
11	...	...	0.05

CASE IV.—G. 0.5 gram salvarsan given October 12th, 1914.

No. of Days after Salvarsan.		Milligrams of As ₂ O ₃ in 100 c.cm. Urine.	
2	...	...	0.4
4	...	...	0.2
7	...	...	0.2
10	...	...	0.15
13	...	...	0.1

CASE IV (continued).—0.5 gram salvarsan given October 29th, 1914.

No. of Days after Salvarsan.		Milligrams As ₂ O ₃ in 100 c.cm. Urine.	
4	...	...	0.4
7	...	...	0.4
10	...	...	0.2
13	...	...	0.1
16	...	...	0.03
21	...	...	0.025

CASE V.—T. 0.5 gram salvarsan given November 11th, 1914.

No. of Days after Salvarsan.		Milligrams As ₂ O ₃ in 100 c.cm. Urine.	
3	...	...	1.33
5	...	...	0.8
8	...	...	0.33
11	...	...	0.12

CASE VI.—F. 0.5 gram salvarsan given October 12th, 1914.

No. of Days after Salvarsan.		Milligrams As ₂ O ₃ in 100 c.cm. Urine.	
2	...	...	1.33
4	...	...	0.4
7	...	...	0.16
10	...	...	0.11
13	...	...	0.023

II. Analysis of Milk.

CASE I.—This was kindly sent by Dr. McIntosh and Dr. Fildes, of the London Hospital. The mother was suffering from ulceration of the throat and a macular rash of two months' duration. Her child, aged 5 months, had a rash on the body and well-marked enlargement of the spleen. On March 13th, 1911, the mother received 0.4 gram salvarsan intravenously, on March 16th 0.5 gram salvarsan intravenously, and on March 21st 0.6 gram salvarsan intramuscularly. The child was suckled all the time.

All symptoms of syphilis in the mother and child rapidly cleared up within five days of the second injection.

Analysis of samples of milk from the mother taken

(a) Seventy-two hours after the first injection,

(b) Twelve hours after the second injection,

showed in the first case (a) the merest trace of arsenic—0.006 mg. of As₂O₃ per 100 c.cm. milk. In (b) no trace of arsenic was present.

CASE II.—B. A mother suffering from syphilis received on March 8th, 1912, 0.5 gram salvarsan given intravenously, on March 27th 0.6 gram, and on April 17th 0.6 gram.

Samples of milk were collected: (a) Five and a half hours, (b) ten and a half hours, (c) sixteen hours, (d) forty hours, and

(e) eighty-eight hours after the first injection. All of these samples were entirely free from arsenic.

III. Analyses of Blood.

CASE I.—"S.," kindly sent by Dr. A. Fleming, May, 1914; 0.6 gram salvarsan given intravenously. Blood taken one hour after injection. On analysis 0.33 mg. of arsenic (As₂O₃) were found in 100 grams of blood.

CASE II.—"B.," kindly sent by Dr. A. Fleming; 0.6 gram salvarsan given intravenously July 1st, 1914. Blood drawn off one hour after injection. The serum was separated from the clot. In 100 c.cm. of serum 0.5 mg. of arsenic (As₂O₃) were found. The clot contained no arsenic.

IV. Cases in which Death occurred after the Administration of Salvarsan or Neo-salvarsan.

CASE I.—A. E., aged 12. Case of congenital syphilis with ascites and cirrhosis of liver. Salvarsan was given, 0.3 gram on September 1st, 1911, and 0.3 gram on September 8th, 1911. The patient died on September 16th, 1911. Death was not accelerated by the administration of the salvarsan, since this was given as a last resort, the condition of the patient being hopeless before its administration. The liver contained arsenic corresponding to 2.5 mg. per 100 grams.

CASE II.—A female, aged 23, suffering from secondary syphilis. Given 0.4 gram salvarsan on November 30th, 1911, and 0.4 gram on December 4th, 1911.

A rise of temperature occurred after the first injection, and also after the second. On December 7th epileptiform convulsions occurred, and coma supervened. The urine contained much albumin, death occurring on the same day after a few hours.

Post-mortem examination showed fatty degeneration of the heart muscle, and cloudy swelling, with focal necrosis of the liver. Analysis showed that the liver contained arsenic in amount corresponding to 0.83 mg. per 100 grams.

CASE III.—A patient suffering from symptoms of syphilitic meningitis. On admission to hospital on August 28th, 1912, he was stuporose. He complained of headache and pain at the back of the neck. Vomiting occurred. There was ptosis of the right eyelid, and weakness of the right side of the face. Both plantar reflexes were extensor. The Wassermann reaction of the blood was positive; that of the cerebro-spinal fluid negative. On August 30th 0.5 gram of salvarsan was given intravenously. Collapse occurred four hours after, and death twenty-nine hours later.

Post-mortem examination showed that death was due to haemorrhage from a small aneurysm of the basilar artery. Analysis showed that in the liver arsenic was present in amounts corresponding to 4 mg. per 100 grams; in the brain only a mere trace was present—0.01 mg. per 100 grams.

CASE IV.—G. Tertiary syphilis. In January, 1913, 0.4 gram of salvarsan was given intravenously; there was some collapse a few hours after, but the patient recovered quickly, and was well in twenty-four hours. On July 26th, 1913, 0.4 gram of salvarsan was given intravenously; the patient was quite well after twenty-four hours, but on July 30th, 1913, the patient was seized with acute abdominal pain and pain at the back of the neck at 10 a.m. At 12.30 p.m. he was comatose and collapsed; at 5.45 p.m. he was in the same condition, with some oedema of legs. Death occurred at 9 p.m.

A post-mortem examination was made by Dr. Salusbury Trevor, and the case was regarded as one of salvarsan poisoning.

CASE V.—Tertiary syphilis with gummata of legs. 0.6 gram salvarsan given on May 9th, 1914, caused no toxic symptoms. On May 23rd 0.6 gram salvarsan given; a rise of temperature and shivering occurred in the evening. On May 25th aphasia occurred, and later coma supervened, with convulsions and death at 10 p.m.

Post-mortem examination by Dr. Spilsbury showed some thickening of pia mater and arachnoid membrane in the brain. The heart showed very advanced fatty degeneration. A small gumma was present in the lower lobe of the left lung. The liver showed advanced fatty degeneration of the cells in the centre of the lobules. The kidneys were enlarged and showed cloudy swelling.

Analysis showed:

Liver:	1.1 milligrams of arsenic as As ₂ O ₃ per 100 grams.
Kidney:	0.2 milligram of arsenic per 100 grams.
Spleen:	2 milligrams of arsenic per 100 grams.
Brain:	No arsenic present.
Spinal Cord:	No arsenic present.
Stomach Contents:	0.08 milligram of arsenic (As ₂ O ₃) per 100 c.cm.
Aorta:	0.025 milligram of arsenic per 100 grams.

CASE VI.—M. H., aged 19 (London Hospital case).

On January 3rd, 1913, salvarsan 0.6 gram was given. On January 9th the patient vomited and became comatose; death occurred on January 12th.

Analysis showed:

	Milligrams of Arsenic (As ₂ O ₃) per 100 grams.	
Small intestine	...	0.1
Large intestine	...	0.11
Liver	...	0.16
Kidney	...	0.13
Spleen	...	0.17
Spinal cord	...	? Trace.

CASE VII.—Specimens kindly sent by Dr. McIntosh and Dr. Fildes. The patient had suffered from acute meningo-

encephalitis of syphilitic origin. On May 26th, 1913, epileptiform convulsions and coma occurred. May 29th, 0.9 gram of neo-salvarsan was given. Collapse occurred three and a half hours later, and death in four and a half hours.

Analysis showed:

	Milligrams of Arsenic per 100 grams.
Liver	0.8
Kidney	1.0
Bone	0.07
Muscle	0.06
Blood	0.05
Brain	0.02

CASE VIII.—Dog, weight 24 lb. 3 oz. Neo-salvarsan 0.3 gram was given, and the animal killed twenty-four hours later. Specimens kindly sent by Dr. McIntosh and Dr. Fildes. Arsenic (As_2O_3) was found in the organs as follows:

	Milligrams of Arsenic per 100 grams.
Liver	1.0
Kidney	0.4
Muscle	0.08
Blood	0.1
Brain	Trace only
Bone	Trace only

CASE IX.—Specimens kindly sent by Dr. McIntosh and Dr. Fildes. The patient was admitted to hospital suffering from secondary syphilis and acute nephritis on May 27th, 1913. On June 20th 0.9 gram neo-salvarsan was given; no ill effects followed. On June 27th 0.9 gram neo-salvarsan was given. On June 29th there was severe headache; on June 30th restlessness and drowsiness; on July 1st convulsion, coma, and death.

Analysis showed the presence of arsenic in the organs as follows:

	Milligrams of Arsenic per 100 grams.
Liver	0.2
Kidney	1.55
Muscle	0.03
Blood	0.02
Brain	Trace only
Bone	Trace only
Suprarenal gland	? Trace
Skin	Nil
Aorta	Nil

It is interesting to note that in this case, in which acute nephritis was present, a very high relative percentage of arsenic was found in the kidney.

CASE X.—Specimens kindly sent by Dr. McIntosh and Dr. Fildes. An infant, aged 3 weeks, suffering from severe symptoms; there was a marked nummular eruption on the arms and legs, and pemphigus was present on the hands and feet. There was ulceration and discharge from the nose. On March 28th, 1911, salvarsan 0.02 gram was given; on March 30th 0.04 gram; and on March 31st 0.04 gram, on each occasion intravenously. Death occurred on April 1st, 1911.

Analysis showed the presence of arsenic in the organs as follows:

	Milligrams of Arsenic (As_2O_3) per 100 grams.
Liver	0.4
Kidneys	0.49
Spleen	0.39
Suprarenal gland	0.17
Lung	0.03
Brain	Absent

For kindly co-operation and help in the work detailed in this paper we are greatly indebted to Dr. J. McIntosh and Dr. Paul Fildes, of the London Hospital; to Dr. B. H. Spilsbury, of St. Mary's Hospital; and to Dr. A. Fleming, of St. Mary's Hospital, London.

REFERENCES.

¹ McIntosh, Fildes, and Dearden, Salt Fever in the Treatment of Syphilis by "606," *Zeit. für Immunitätsforschung*, January, 1912; also *Lancet*, March 9th, 1912. ² McIntosh and Fildes, the Fixation of Arsenic by the Brain after Intravenous Injection of Salvarsan, *Proc. Roy. Soc., B*, vol. lxxviii, 1914.

MAJOR W. L. KELLER, Medical Corps, U.S.A., has, we learn from the *Military Surgeon* for February, sent to the Surgeon-General of the United States Army a communication in which he says that he treated many varieties of sciatica during the past year, and has found no treatment so useful as the injection of novocain into the sacral canal through the hiatus sacralis; 4 c.cm. of a 5 per cent. solution was dissolved in 100 c.cm. of normal salt solution and sterilized by boiling. The patient was placed in the knee-chest position, and the region of the sacrum and coccyx rendered sterile by iodine. A needle from 6 to 10 cm. long, attached to a large glass syringe, was used to inject from 60 to 120 c.cm. of the solution. One injection gave absolute relief in the majority of cases, but three or four might be required. The effect was immediate, and the patient could usually walk without pain or limping when he left the table.

A CASE OF GAS GANGRENE EXHIBITING UNUSUAL PROOFS OF A BLOOD INFECTION.

BY

G. T. MULLALLY, AND J. W. McNEE,
F.R.C.S.ENG., M.D.

CAPTAINS R.A.M.C.

(From a Casualty Clearing Station and a Mobile Laboratory, France.)

THIS case is reported because it presented, in an unusual and convincing way, proofs of the occurrence of a blood infection with gas-forming organisms. No similar case has occurred in our considerable experience of gas gangrene, nor have we heard of any other like it. The essential facts may be given at once:

Private —, Argyll and Sutherland Highlanders, was wounded late at night on March 18th, 1915, by a bullet which entered the right arm, fracturing the humerus. Gas gangrene developed in this wound on March 21st—that is, two and a half days after the injury. As the man passed through a field ambulance on March 19th he received the usual antitetanic injection, below the left nipple, and was thereafter evacuated at once to a casualty clearing station. On March 20th he complained of pain at the site of the serum inoculation, and by March 21st a definite patch of gas gangrene had appeared there. On March 20th, the day after admission to the casualty clearing station, a hypodermic injection of pituitrin was made into the left forearm to combat collapse. By March 22nd the site of this puncture showed also an area of gas gangrene.

From these three places (right arm, left pectoral region, and left forearm) and also from the blood the same type of gas-forming organism was isolated by cultures made on March 22nd. This organism was of the "malignant oedema" type, most of the bacilli showing central spores.

The arm was amputated on March 24th, and the man made a good recovery, being evacuated to the base on March 27th. Subsequently information was received that he made good progress for some time, but later developed "pneumonia," from which he died on April 17th, a month after the original wound.

A brief account of the clinical features and the bacteriological findings are given below, in detail, to complete the record of the case.

The important facts in this case seem to be:

1. The rapid appearance of gas gangrene at three distant sites in the body. It is evident that the slight local injuries caused by the antitetanic injection at the field ambulance and the hypodermic injection of pituitrin at the casualty clearing station, offered suitable foci for organisms circulating in the blood stream to come to rest and develop.

2. Bacteriological evidence was obtained of what had been proved to us in nature—namely, that the gas-forming organisms had invaded the blood stream.

3. The fact that the man recovered from this severe infection sufficiently to be transferred to the base three days after the arm was amputated is in itself remarkable.

Private —, Argyll and Sutherland Highlanders, was wounded in the right arm on March 18th, 1915, and admitted to a casualty clearing station next day. When admitted he was in a state of profound collapse and almost pulseless. The bullet had entered the back of the right upper arm, and emerged in front and to the inner side, making a large ragged wound. The humerus was fractured, and the brachial artery torn across. Antitetanic serum had been injected at a field ambulance before admission. On the following day he was rather better, and the wound was thoroughly syringed out with peroxide solution. Towards evening he collapsed again and became almost pulseless. The wound was dressed, and at this time showed no definite evidence of gas gangrene. Although somewhat delirious, he now began to complain of pain in the left pectoral region, where the antitetanic injection had been given. Next morning a little crackling was felt over this area, but this was at first put down to air having, perhaps, been injected along with the serum. Owing to the collapse, he was given during the night a hypodermic injection of pituitrin into the left forearm. On March 21st his general condition was unchanged, but a large patch of gas gangrene was now evident on the inner side of the right arm and forearm, below the exit wound. Another patch of gangrene was also found on the left side of the chest, including the area of the antitetanic injection. Both gangrenous areas were freely incised and dressed with peroxide solution. The affected area on the chest wall